Medical and Pediatric Oncology 27:74–78 (1996)

Gonadal Function Following Chemotherapy for Childhood Hodgkin's Disease

E.J. Mackie, MB, MRCP, M. Radford, MD, FRCP, and S.M. Shalet, MD, BSc, FRCP

Gonadal function was assessed in 101 postpubertal subjects after chemotherapy for childhood Hodgkin's disease. All had received ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisolone) chemotherapy alone, with no radiotherapy below the diaphragm. Gonadotropin levels were available in 46 (79.3%) male and 32 (74.4%) female subjects. The mean age at diagnosis in the male cohort was 12.2 years (range 8.2–15.3) and in the females 13.0 years (9.0–15.2). The males and the females were studied at a median of 6 years (range 2.5–11.1) and 4.3 years (range 1.9–11.5) from diagnosis, respectively.

Forty-one (89.1%) male subjects had elevated follicle-stimulating hormone (FSH) levels, confirming severe germinal epithelial damage. Germinal epithelial damage was seen in subjects up to 10 years out of therapy. Subtle Leydig cell dysfunction was identified in 24.4% with raised luteinizing hormone (LH) levels. All subjects, however, progressed spontaneously through puberty.

Seventeen (53%) women had raised gonadotropin levels, with variable estradiol levels. Of these, 10 subjects presented with symptomatic ovarian failure and 6 received hormone replacement therapy (HRT). Nine women had 11 successful pregnancies, two of whom had previously had symptoms of ovarian failure with one requiring HRT. A much higher prevalence of ovarian failure has been observed, than has previously been considered in the prepubertal and pubertal female following combination chemotherapy. These conclusions have important implications for future counseling, management, and research in this population.

Key words: Hodgkin's disease, gonadal toxicity, chemotherapy

INTRODUCTION

In Hodgkin's disease (HD), overall survival rates greater than 90% are reported [1]. However, this improved prognosis is not without long-term consequences, including the potential for severe gonadal damage.

Germinal epithelial dysfunction is well documented in adult males receiving combination chemotherapy, with reports of azoospermia, raised gonadotropin levels, and histological evidence of germinal aplasia [2–5]. Several studies have identified similar findings following both childhood and adolescent HD [6–8] with evidence of dose-related testicular damage [9]. Subtle Leydig cell dysfunction has also been documented, despite clear evidence of spontaneous progression through puberty [6,8,9]. The longer-term clinical implications of this damage are yet to be defined.

In the adult female, ovarian function appears to be less severely affected by chemotherapy, although there is a clear correlation between cytotoxic-induced ovarian damage and increasing age at treatment [10–13]. Ovarian function in the prepubertal and pubertal female is less certain, with limited studies demonstrating the resilience of the ovary to chemotherapy [6,7,14,15]. Recent evidence, however, has identified a nine-fold risk of developing premature menopause after treatment with alkylating agents during adolescence, with the associated problems of mood changes, dyspareunia, and osteoporosis [16].

With uncertainty over the quality of ovarian function following treatment for childhood HD, the importance of further assessing female reproductive potential is highlighted. The present study therefore examines both testicular and ovarian function in a large series of children treated for HD with combination chemotherapy.

MATERIALS AND METHODS

Assessment of gonadal function was recommended as part of follow-up for subjects entered into the United Kingdom Children's Cancer Study Group (UKCCSG) HD Trial 8201. All subjects who had completed puberty by January 1992 were evaluated. Any patient receiving

From the Department of Paediatric Oncology, The Christie Hospital, NHS Trust (E.J.M.), Manchester, Department of Paediatric Oncology, Southampton General Hospital (M.R.), Southampton, and Department of Endocrinology, The Christie Hospital, NHS Trust (S.M.S.), Withington, United Kingdom.

Received March 17, 1995; accepted October 3, 1995.

Address reprint requests to Professor S.M. Shalet, Department of Endocrinology, The Christie Hospital, NHS Trust, Wilmslow Road, Manchester M20 9BX, U.K.

either radiotherapy below the diaphragm or alternative chemotherapy to ChlVPP (chlorambucil, vinblastine, prednisolone, and procarbazine) was excluded from this analysis. This combination chemotherapy was given for a recommended minimum of six courses (equivalent to 504 mg/m^2 chlorambucil and 8,400 mg/m^2 procarbazine) or a maximum of eight courses.

Of the 368 subjects entered into HD 8201, 168 (45.7%) were postpubertal by January 1992. One hundred and one subjects were evaluable, 43 (42.6%) females and 58 (57.4%) males. The mean age at diagnosis in the female cohort was 13.0 years (range 9.0–15.2) and in the males 12.2 years (range 8.2–15.3).

Testicular function was assessed by examination of testicular size with a Prader orchidometer, basal follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone levels, and semen analysis.

A menstrual and pregnancy history provided initial assessment of ovarian function, alongside the presence of menopausal symptoms such as hot flushes, dysparuenia, irritability, and difficulty with sleeping. Further evaluation was obtained by estimation of basal FSH, LH, and estradiol levels, with a day 21 progesterone level in those with a regular menstrual cycle. Amenorrhea was defined by the absence of menses for 6 months or more and oligomenorrhea as a severely irregular cycle for at least a similar 6-month period.

All serum gonadotropin levels were measured by standard radioimmunoassays.

The two groups with and without postpubertal assessments were compared according to amount of chemotherapy received, sex, and pubertal stage at diagnosis. Tables were formed for the categorical variables and appropriate summary statistics calculated for the ordered variables. The chi squared and Mann Whitney tests were used to examine statistical significance. Multiple regression analyses were used to examine the relationship of serum gonadotropin levels with sex, amount of chemotherapy received, pubertal status at diagnosis, and time from diagnosis to assessment. Statistical significance was assessed with the standard F-test.

RESULTS

Gonadotropin levels were available in 46 (79.3%) male and 32 (74.4%) female subjects, with a median time from diagnosis to assessment of 6 years (range 2.5–11.1) and 4.3 years (range 1.9–11.3), respectively (Table I). No marked differences were found between the two groups with and without postpubertal assessments, except for female pubertal status at diagnosis, in that 31% (n = 10) were postpubertal in the assessed group, compared with those without data, who were all prepubertal or pubertal at diagnosis (n = 11).

Male Cohort

Forty-one (89.1%) subjects had elevated FSH levels (range 10.8–40.7 IU/l); upper limit of normal = 10 IU/l (Fig. 1). No association was identified between raised FSH levels and age or pubertal status at time of receiving chemotherapy or time elapsed since treatment. Testicular volumes were reported in 25 (53%) subjects, all of whom had raised FSH levels and small testes (<15 ml). Azoospermia was present in the seven subjects in whom semen analysis was performed. These seven were treated at a median age of 13 years (range 9.9–14.7) and completed chemotherapy a median of 5.5 years (range 1–8.3 years) prior to analysis. Leydig cell function was less affected by chemotherapy. All subjects progressed spontaneously through puberty.

Testosterone levels (range 4.3–37.8 nmol/l; normal range = 10–30 nmol/l) were available in 37 of the 41 subjects were raised FSH levels; 5 showed low testosterone levels. A raised LH level (range of 10.3–18 IU/l; upper limit of normal = 10 IU/l) was identified in 10 (24.4%) subjects (Fig. 1), all of whom had elevated FSH levels. No association was seen between abnormal Leydig cell function and age at treatment, amount of chemotherapy received, or time of assessment from treatment.

Female Cohort

All gonadotropin results reported were in the follicular phase of the menstrual cycle (normal ranges defined in Table II), including one subject who also had an estradiol level in the normal luteal range, regular menses, and a day 21 progesterone indicating ovulation (40 nmol/l). Of the 10 subjects with symptomatic ovarian failure, all had elevated FSH levels (range 19–130 IU/l), but in only 3 were the estradiol levels less than 100 pmol/l (Table II). A further 7, without symptoms of ovarian dysfunction, had raised FSH levels (range 16–30 IU/l), of whom 5 had variable LH (range 6.1–24 IU/l) and estradiol levels (range 61–147 pmol/l). The other 15 subjects had normal FSH (range 1–7.1 IU/l), LH (range 1.3–6.9 IU/l), and estradiol levels (range 140–560 pmol/l). No association was seen between FSH levels and age at chemotherapy or time between analysis and treatment. Hormone replacement therapy (HRT) was given to six of the symptomatic subjects, three with estradiol levels less than 100 pmol/l (Table II). Nine subjects have had 11 successful pregnancies at a mean age of 21.9 years (range 18–24) and a mean time of 6 (range 4–9) years from completion of therapy. Of these, one had previously received HRT.

DISCUSSION

The long-term consequences of combination chemotherapy on gonadal function have been well defined in

TABLE I. Gonadotropin Levels and Pubertal Status at Diagnosis

Pubertal status at diagnosis	Sex	Number	FSH (IU/l) Median (range)	LH (IU/l) Median (range)	Testosterone (nmol/l) Median (range)	Estradiol (pmol/l) Median (range)
Prepubertal	Male	14	18.7 (5.2–40.7)	6.5 (4.9–12.5)	10.9 (4.3–30.0)[a]	—
Pubertal	Male	32	15.6 (1.0–32.0)	7.8 (2.2–18.0)	16.0 (6.1–378)[b]	—
Prepubertal	Female	7	20 (3.5–70.9)	5.8 (2.3–10.9)[a]	—	118.5 (81–420)[a]
Pubertal	Female	15	7.1 (10–130)	5.8 (1.3–103.6)[a]	—	204 (40–560)[c]
Postpubertal	Female	10	13 (2.0–42)	11 (3–50)[a]	—	164 (52–280)[d]

Data missing: a = 1, b = 4, c = 3, d = 2.

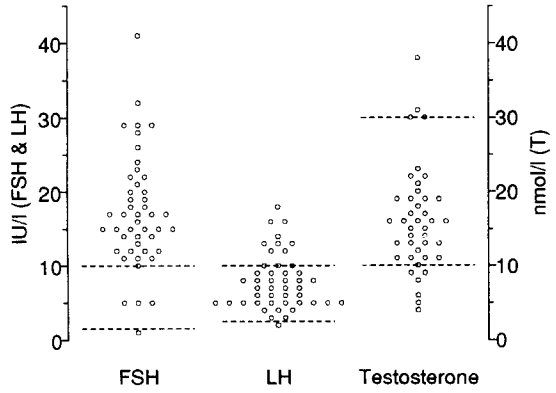

Fig. 1. The values of serum FSH, LH, and testosterone in postpubertal male subjects. Normal ranges are indicated.

adult HD, but less is known regarding childhood-treated HD. In this study, we have demonstrated germinal epithelial damage 10 years out of therapy, subtle Leydig cell damage in 24.4%, and a much higher incidence of ovarian damage than has been previously reported. These findings have important implications in the assessment, management, and counseling of this population.

Historically, initial reports of chemotherapy-induced gonadal damage date back to 1948 following the use of nitrogen mustard [17]. Since then, gonadal toxicity has been attributed to other chemotherapeutic agents, both in combination and as single agents [18–20].

Although sustained testicular germinal epithelial damage following childhood HD has been documented in several studies [7,8], occasional long-term recovery of spermatogenesis has also been reported [7]. Our results confirm severe, germinal epithelial dysfunction following ChlVPP chemotherapy, with abnormalities in those now 10 years out of therapy. The number with semen analysis was limited, but there is good evidence correlating a persistently raised FSH level with severe germ cell damage [4,9]. Thus, our FSH results imply that the damage to the germinal epithelium is likely to be permanent.

Leydig cell function remains largely intact, with our cohort progressing through puberty without need for androgen replacement therapy. Shafford et al. [8] noted that 57% of their cohort receiving combination chemotherapy had an elevated serum LH level. Our cohort demonstrated similar, subtle Leydig cell dysfunction, with a raised LH level in 24.4%. The long-term consequences of this damage remains uncertain. However, a significant reduction in bone mineral density has been demonstrated by Holmes et al. [21] in adult males who have received chemotherapy for HD. A significant positive correlation existed between the serum testosterone level and the integral bone mineral density. Therefore, chemotherapy-induced Leydig cell damage of a subtle nature has been identified as a possible cause of the osteopenia; this highlights the importance for continued prospective follow-up of those treated in childhood, when peak bone mass is being acquired. Clark et al. [22] have recently reported sexual dysfunction in 31% of adult men following completion of chemotherapy for HD, with two achieving symptomatic benefit from androgen therapy, again indicating clinically significant Leydig cell dysfunction.

Long-term follow-up of ovarian function following combination chemotherapy for childhood-treated HD has been limited. Bramswig et al. [23] assessed the ovarian function in 57 postpubertal females treated for HD with chemotherapy, but not pelvic irradiation, during childhood or adolescence. All demonstrated normal ovarian function as judged by the gonadotropin responses to a standardized intravenous gonadotropin releasing hormone test.

It is therefore of importance that 27.8% (n = 10) of our female cohort developed symptomatic ovarian failure, with six requiring HRT. Seven of these 10 subjects were either prepubertal or pubertal at the time of receiving chemotherapy. Biochemical ovarian dysfunction was documented in a further seven subjects. These figures suggest a much higher prevalence of ovarian failure than has previously been considered. This has important implications for HRT, in view of the significant increase in risk of osteoporosis in women with secondary amenorrhea of only 6 months duration [24].

It is interesting that ovarian function was only fully documented in the female subjects who were postpubertal at diagnosis. Although this may reflect the greater susceptibility of the ovary to cytotoxic damage in this older group, it is also possible that subjects treated before completion of puberty may eventually progress to symptomatic ovarian failure and present for further investigation.

TABLE II. Gonadotropin Levels, Menstrual, and Pregnancy Status in Female Subjects With Symptomatic Ovarian Failure*

Subject	Pubertal stage at diagnosis	FSH (IU/l)	LH (IU/l)	Estradiol (pmol/l)	Progesterone (nmol/l)	Menses	Time off therapy (years)	HRT	Cycles ChlVPP
1	Prepubertal	70.9	—	81	<5	A	4	Y	6
2	Prepubertal	21	7.7	170	—	O	10.5	Y	8
3	Pubertal[a]	130	103	319	<1	A	2.5	N	6
4	Pubertal	30	49	102	<5	O	1.5	N	6
5	Pubertal	45	58	40	1.6	A	3.75	Y	9
6	Pubertal	19	51	330	—	O	4.2	N	6
7	Pubertal	24	34	—	—	O	2.4	N	9
8	Postpubertal[a]	32	50	150	—	A	1.7	Y	6
9	Postpubertal	42	50	52	—	A	4.8	Y	8
10	Postpubertal	40	47	166	—	A	1.25	Y	8

*A = amenorrheic; O = oligomenorrheic. Normal values: FSH — follicular phase 2–8 IU/l, postmenopausal >34 IU/l; LH — follicular phase 2–12 IU/l, postmenopausal >25 IU/l; estradiol — follicular phase 75–250 pmol/l, mid-cycle 450–1,500 pmol/l, luteal phase 350–850 pmol/l, postmenopausal <100 pmol/l; progesterone — follicular phase <5 nmol/l, luteal peak >25 nmol/l.
[a]Pregnancy (both 4 years off therapy).

Serial follow-up of this cohort will therefore be important in order to assess whether ovarian function eventually recovers or whether progression to a premature menopause is inevitable.

It is too early to give a full account of pregnancy outcome, but seven women in this study have now achieved 11 normal pregnancies, two of whom had raised gonadotropins prior to conception and one who had previously received HRT. At present, there is no indication either in this cohort or in the literature of an increased number of abnormalities in the offspring or an increase in the incidence of miscarriages following combination chemotherapy.

Serial studies in those treated for childhood HD are now imperative to gain a more complete understanding of the long-term effects on gonadal dysfunction, including the wider implications of this damage, such as bone mineral density loss and the true prevalence of premature menopause following chemotherapy. Despite the increased survival in childhood-treated HD, significant physical and psychological morbidity is seen in association with gonadal dysfunction and it is therefore essential that we are able to advise these individuals appropriately in our follow-up clinics.

ACKNOWLEDGMENTS

We thank David Ryder of the Medical Statistics Department, Christie Hospital, NHS Trust, for performing the statistical analyses. We also acknowledge the UKCCSG Centres that provided data for this study.

REFERENCES

1. Radford M, Barrett A, Martin J: Treatment of Hodgkin's disease in children. Med Pediatr Oncol 19:400, 1991.
2. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG: The effects of Hodgkin's disease and combination chemotherapy on gonadal function in the adult male. Cancer 49:418–422, 1982.
3. Waxman JHX, Terry YA, Wrigley PFM, Malpas JS, Rees LH, Besser GM, Lister TA: Gonadal function in Hodgkin's disease: Long-term follow-up of chemotherapy. Br Med J 285:1612–1613, 1982.
4. Kreuser ED, Xiros N, Hetzel WD, Heimpel H: Reproductive and endocrine gonadal capacity in patients treated with COPP chemotherapy for Hodgkin's disease. J Cancer Res Clin Oncol 113:260–266, 1987.
5. Chapman RM, Sutcliffe SB, Malpas JS: Male gonadal dysfunction in Hodgkin's disease. JAMA 245:1323–1328, 1981.
6. Whitehead E, Shalet SM, Morris Jones PH, Beardwell CG, Deakin DP: Gonadal function after combination chemotherapy for Hodgkin's disease in childhood. Arch Dis Child 47:287–291, 1982.
7. Sy Ortin TT, Shostak CA, Donaldson SS: Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: The Stanford experience. Int J Radiat Oncol Biol Phys 19:873–880, 1990.
8. Shafford EA, Kingston JE, Malpas JS, Plowman PN, Pritchard J, Savage MO, Eden OB: Testicular function following the treatment of Hodgkin's disease in childhood. Br J Cancer 68:1199–1204, 1993.
9. Bramswig JH, Heimes U, Heiermann E, Schlegel W, Nieschlag E, Schellong G: The effects of different cumulative doses of chemotherapy on testicular function. Cancer 65:1298–1302, 1990.
10. Horning SJ, Hoppe RT, Kaplan HS, Rosenberg SA: Female reproductive potential after treatment for Hodgkin's disease. N Engl J Med 304:1381, 1981.
11. Chapman RM, Sutcliffe SB, Malpas JS: Cytotoxic-induced ovarian failure in women with Hodgkin's disease. JAMA 242:1877–1881, 1979.
12. Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT: Long-term follow-up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. Am J Med 71:552–556, 1981.
13. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG: The effect of combination chemotherapy on ovarian function in women treated for Hodgkin's disease. Cancer 52:988–993, 1983.
14. Stillman RJ, Schinfeld JS, Schiff I, Gelber RD, Greenberger J, Larson M, Jaffe N, Li PJ: Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol 139:62–66, 1981.
15. Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD,

Krauss MR, Steinhorn SC, Hassinger DD, Austin DF, Bragg K, Holmes GF, Holmes FF, Latourette HB, Weyer PJ, Wister Meigs J, Teta J, Crook PHJW, Strong LC: Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 317:1315–1321, 1987.

16. Byrne J, Fears TR, Gail MH, Pee D, Connelly RR, Austin DF, Holmes GF, Holmes FF, Latourette HB, Wister Meigs J, Strong LCC, Myers MH, Mulvihill JJ: Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol 166:788–793, 1992.
17. Spitz S: The histological effects of nitrogen mustards on human tumours and tissues. Cancer 1:383–398, 1948.
18. Louis J, Limarzi LR, Best W: Treatment of chronic granulocytic leukaemia with myleran. Arch Intern Med 97:299–308, 1956.
19. Watson AR, Rance CP, Bain J: Long term effects of cyclophosphamide on testicular function. Br Med J 291:1457–1460, 1985.
20. Guesry P, Lenoir G, Broyer M: Gonadal effects of chlorambucil given to prepubertal and pubertal boys for nephrotic syndrome. J Pediatr 92:299–303, 1970.
21. Holmes SJ, Whitehouse RW, Clark ST, Crowther DC, Adams JE, Shalet SM: Reduced bone mineral density in men following chemotherapy for Hodgkin's disease. Br J Cancer 70:371–375, 1994.
22. Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM: Gonadal function following chemotherapy for Hodgkin's disease—a comparative study of MVPP and a seven drug hybrid regimen. J Clin Oncol 13:134–139, 1995.
23. Bramswig JH, Heiermann E, Heimes U, Schlegel W, Hanker JP, Schellong G: Ovarian function in 63 girls treated for Hodgkin's disease (HD) according to the West-German DAL-HD-78 and DAL-HD-82 therapy study. Med Pediatr Oncol 17:344, 1989.
24. Davies MC, Hall ML, Jacobs HS: Bone mineral loss in young women with amenorrhoea. Br Med J 301:790–793, 1990.